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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,766	07/06/2001	Goran Forsberg	P02188US0 (10104199)	7699

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,766	FORSBERG ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,22-30,34,53,60-68,72,93-97 and 99-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 22-30, 34, 53, 60-68, 72, 93-97, 99-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 6-2-04 and 9-27-04 have been entered.

Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, 99-106 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Any rejections not reiterated herein are withdrawn in view of the new rejections set forth below.

New Rejections Based on Amendment

Claims 15, 22-25, 26-29, 34, 60-63, 64-67, 72, 93-97 and 99-101 and 103-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to independent claims 15, 22, 53, 60, 93 and 94, Applicant has amended the claim to recite "..the amino acid position in region C to be replaced is at least selected from the group consisting of 74, 75, 76, 77, 78, 79, 80, 81, 82, 83 and 84..". Previously, Applicants have argued on the record that region C is defined in Figure 4 and has 11 amino acids. The wording of the claims indicate that region C "is at least", but can be more. The concept presented by this language in the claims is that region C is more than the recited

positions and not limited to the 11 positions described in Figure 4 as argued by Applicants. This open-ended definition is not supported by way of written description in the specification as filed. The same issue appears in claim 22 with region "E". Additionally, seroreactivity was determined in the context of by SEA/E-18. The current claims do not define any mutant in region C alone that has reduced seroreactivity. There is no conception of mutations in region C alone, that provide for the generic reduced seroreactivity, in all cases set forth in Table 1, page 44, seroreactivity is compared to SEA/E-18 and is only viewed as a combination of region C mutations with mutations in other regions. The specification does not teach reduced seroreactivity for individual mutations in Region C alone of SEE as is now claimed. The dependent claims 23-25, 27-29, 34, 61-63, 65-67, 72, 95-97 and 99-101 and 103-106 are likewise new matter.

As to claims 26 and 64, Applicants have redrafted the claim as an independent claim and have removed the limitation of what the antibody moiety binds to. As such, the scope of the claims now includes non-cancer cell directed antibodies. The written description of the specification as filed does not support this breadth. These passages do not provide for conception of the broad genus of antibody moieties as now claimed. The courts have addressed a similar issue in *In re East and Harmon* (CCPA) 181 USPQ 716 (May 9, 1994) wherein the claims of a reissue application were drawn to new matter since they broadly recite genus of "carrier particles" which is not disclosed in original patent, which discloses only subgenus of "magnetic carrier particles" and species of "iron, ferrites, nickel, and cobalt" carrier particles. Here, the specification broadly discusses cancer directed antibodies (i.e. lung, breast, colon, kidney, pancreatic, ovarian, stomach, cervix and prostate) and specifically discloses the species of lung antibody. If the written description does not use precisely the same terms used in a claim, the question then is whether the specification directs or guides one skilled in the art to the subject matter claimed. See, e.g., *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). It has been analogized that the requirement that the written description direct one to the

claimed subject matter to "blaze marks" on specific trees that mark a trail through a forest. See *In re Ruschig*, 154 USPQ 118, 122 (CCPA 1967). It has been found that without such specific direction, a general disclosure will not be sufficient to support narrowly claimed subject matter. See *Fujikawa v. Wattanasi*, 39 USPQ2d 1895, 1905 (CAFC 1996). There is no direction or "blaze marks" to broad antibodies that encompass antibodies to pathogens such as bacteria, toxins, fungal antigens, parasitic antigens, etc. and disease to be treated, outside of a reference to cancers. The reference to cancers and the particular type of cancers does not lead one skilled in the art to the broad genus of antibody moiety, which includes a plethora of non-cancer associated cell surface antigen. As such, it cannot be concluded that Applicants conceived of and were in possession of the now claimed subject matter, at the time of filing. Further, it is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, 99-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to products and pharmaceutical compositions comprising a mutated Staphylococcal enterotoxin E superantigen comprising replacement mutations wherein at least one amino acid in Region C is replaced, dependent claims further comprise substitutions in region E conjugated to an antibody moiety that binds a cancer-associated cell surface structure or undefined antigen. The entirety of the written description of the specification is drawn to use of the bacterial superantigen conjugates is for

treatment of cancer and fails to teach any use for generic antibody conjugates that are not directed to cancer antigens.

The teachings of the specification with respect to mutations at different positions are limited to Table 1 on page 44. The specification fails to provide written description and characterization of individual mutations in region C as it relates to the base structure of now claimed Staphylococcal enterotoxin E. The specification at page 44, Table 1, compares multiple mutations of different positions in SEE as compared to an already mutated SEA-E-18 and NOT to SEE *per se* (see specification paragraphs [0161 and 0163]. Table 1 does not set forth the contribution of any one of the claimed substitutions or any combination thereof with respect to reduced seroreactivity or superantigen antibody dependent cellular cytotoxicity (SADCC). There is no written description of the effect of individual mutations of region C on the seroreactivity or SADCC activity of the superantigen and no description of the effect of substitutions on claimed positions 76, 77, 80, 82 and 83. The one of skill in the art could not make substitutions of "at least one" that meet the limitation of "reduced seroreactivity" or that have SADCC. The art specifically teaches that "Although the amino acid sequences of SEA and SEE are very similar, there are differences in biological function. The Vβ-specificity for SEA and SEE differ (2, 17) as so their affinities to Different MHC class II alleles (9), and SEA may also have a different affinity for the TCR than SEE (16). Interestingly, in many cases chimerical molecules of SEA and SEE acquire properties that are unique and not the predicted combinations between SEA and SEE (Figs. 5-7).") Cavallin et al (The Journal of Biological Chemistry, 275(3):1665-1672, 2000; see page 1671, column 1, third full paragraph; of record). Clearly, random substitution into regions of SEE does not have a predictable outcome on the biological properties even when combined with a highly similar molecule SEA, another superantigen. The art specifically teaches that "..C215FAb-SEA but not C215Fab-SEE, induced T cell cytotoxicity and proliferation in these MHC class II-independent systems..." and "Introduction of a region from SEA, comprising amino acids 20-27, to SEE

transferred the ability to engage T cells in the absence of MHC class II..." (Antonsson et al, 1997, see abstract ; of record). As such, it appears that the region of amino acids 20-27 of SEA must be transferred to SEE and are *required to generate SADCC* in any SEE mutant and the claims are not so limited. In the absence of these amino acid substitutions it is clear that any SEE mutant would not be expected to have SADCC. It is further unclear as to what if any MHC class-II independent activity any combination of mutations of SEE regions C and E the mutant would possess. There is no teaching in the specification that mutated SEE alone has SADCC activity or activity sufficient for tumor killing *in vivo*. SADCC activity is required for activation of T-cells and killing of target cells in vitro and *in vivo*. Absent this activity present in the mutated superantigen, it would not be an effective T-cell targeting moiety and would not direct T cells to kill tumor cells either *in vitro* or *in vivo*. There is no teaching in this specification as filed, that such a conjugate would effectively provide for superantigen antibody dependent cellular cytotoxicity toward tumor cells. Further, SEE and variants thereof have a markedly reduced ability as compared to SEA to induce T-cell proliferation (see Cavallin et al, page 1671, column 1; of record) and the specification does not teach that any of the claimed SEE variants resolves this problem. The specification is devoid of written description methodology as how to make these variants that allow for superantigen antibody dependent cellular cytotoxicity for tumor cells *in vitro* or *in vivo*. Second, the art teaches that "In the context of work with fusion proteins, however, we have found that the ability for T cell MHC class II independent cytotoxicity, superantigen-antibody dependent cell cytotoxicity (SADCC), of SEE conjugates is poor." (Antonsson et al, U.S. Patent No. 6,514,498, column 3, lines 5-10) and is acknowledged at paragraph [0160] of this specification. The art teaches that antibody conjugates with SEE have markedly decreased antibody dependent cellular cytotoxicity (see Antonsson et al, Journal of Immunology, page 4246, column 2, Figure 1; of record) and Antonsson et al (U.S. Patent No. 6,514,498, Figure 6B; of record). It is noted that tumor cells are allegedly killed by superantigen antibody dependent

cellular cytotoxicity (SADCC) and the specification is devoid of any demonstration that the *in vitro* result correlates with efficacy of the SEE chimeric to function similarly *in vivo* to kill lung cancer cells. With respect to claim 93 and dependent claims 97-97, 99-103 and 106, Table 1 of the specificaiton teaches that substitutions into positions 74, 75 and 78 as modified on the SEA/E-18 backbone abolish the SADCC activity (chimeria named SEA/E-75). However, these same mutation sin combination with other mutations provide for an enhanced SADCC activity (chimera named SEA/E-120). As such, the effect of any specific mutation, taken alone or in combination with other mutations even on the same SEA/E-18 backbone does not predict the same outcome on SADCC activity. One skilled in the art cannot simply predict the effect of any one or combination of mutations on SADCC activity. The specificaiton does not teach the effect of single mutations, double mutations of a representative number of combinations of positions from the claimed regions C and E, such that one of skill in the art would be able to make and use mutant SEE superantigen conjugates effective for treatment of cancer. In applications directed to inventions in arts but where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. Additionally, the specification and the art fail to teach therapeutic antibodies for colon, kidney, pancreatic, ovarian, stomach, cervix and prostrate cancer. The specification does not teach cell surface structures associated with these cancers to which antibodies could be made for treatment. There is no written description of such antibodies in the art of record and not

a single reference in the specification to those in the art that would be useful. Furthermore, the art indicates that only SEA and SEB have been demonstrated to induce cell death *in vivo* (Weinrauch et al, Annual Review of Microbiology 53:155-87, 1999; of record). Therefore, one of skill in the art would have reasons to doubt that the antibody conjugates based on SEE could be able to be used in any therapeutic treatment of cancer and lung cancer in particular in the absence of evidence to the contrary. This specification fails to teach the correlation of the claimed mutations of SEE with *in vitro* SADCC, reduced seroreactivity using pooled human IgG with therapeutically effective results in any *in vivo* model of cancer and lung, breast, colon, kidney, pancreatic, ovarian stomach, cervical or prostate cancer in particular. With respect to the particular antibody 5T4, this antibody has not been apparently demonstrated to have efficacy in the treatment of lung cancer by means of this specification and one would have substantial reason to doubt that it could be used in the absence of factual evidence to the contrary. The entirety of the specification is drawn to use of the claimed conjugates for treatment of cancer. None of the conjugates of the invention have been demonstrated to have efficacy in any animal model of cancer and lung cancer in particular. Applicants have not demonstrated the correlation of SADCC in vitro with the 5T4- antibody conjugate with effective therapeutic function *in vivo* in any animal model. Although Applicant has provided a general strategy for the use of the claimed conjugates in cancer therapy, the lack of teaching of the effect of region C mutations of SEE on seroreactivitity and SADCC, the unpredictable nature of the substitution art as recited above and in antibody-mediated cancer therapeutics, the unpredictable effect of any mutation of on SDCC and SADCC *in vitro*, it does not appear that the general teachings for treatment of cancer are sufficient to enable the skilled artisan to make and use the claimed SEE variants as claimed for the treatment of cancer in general or any of the specific cancers recited in the claims. Applicants have not provided the expected range of results, statistics or predictability of the claimed method of use of the SEE mutant part of the conjugate or

the conjugates *per se*, or the proper control conditions for the skilled artisan to practice the claimed invention. Due to the high degree of unpredictability with biotechnology therapeutics and antibody-based cancer therapeutics in general, it is essential that Applicants' invention be demonstrated to work as claimed. In the absence of further guidance on the part of Applicants' it would require undue experimentation to make and use the SEE mutants, and SEE mutant conjugates as claimed for the treatment of cancer.

Claims 15, 22-30, 34, 53, 60-68, 72, 93-97, 99-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 15, 22, 53, 60, 93, 94, the language "is at least selected from the group consisting of" is *prima facie* indefinite. The purpose of Markush language is to define the substitutions by closed language. The viewed purpose of "at least selected" is to open up the Markush group to include more amino acids and more substitutions in the indicated regions. The metes and bounds of the regions have been argued to be defined by Figure 4. The amendment to the claims appears to contradict the record and implies that the region encompasses more than just the recited members of the Markush group. As such, this language is deemed vague and indefinite, because it renders the group open and contradicts Applicants asserted metes and bounds of the regions as set forth in Figure 4. Further, in view of this language, the rejection over the metes and bounds of the regions, not specifically articulated in the claims is maintained. Applicants are arguing Figure 4 metes and bounds but the claims clearly encompass more than the Figure defines. Regions A to E are still not defined in claim 53. Limitations from Figure 4 are not read into the claims because they are in part contradicted by the art of record. The dependent claims 23-25, 27-30, 34, 61-63, 65-68, 72, 95-97 and 99-106 are likewise indefinite.

As to claims 15, 53, 93 and dependent claims 22-25, 27-30, 34, 66-63, 65-68, 72, 94-97 and 99-106, the recitation and reference to particular amino acid positions in the

absence of a particular reference sequence identifier renders the metes and bounds of the claim indefinite. Specific amino acid positions are relative to a defined sequence and the claims do not define the relative sequence.

As to claim 15, 53, 93 and dependent claims 22-25, 27-30, 34, 66-63, 65-68, 72, 94-97 and 99-106, the term "reduced seroreactivity" is *prima facie* indefinite, because the term reduced is a comparative term and the claims do not define the basis for comparison.

As to the composition claims as compared to the product claims, the claims appear to be identical in scope and are indefinte because a compositon is more than a single element and the compositions claim a single element the product. Amendment of the composition to include a second element such as a carrier or excipient would obviate this rejection.

Status of Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645